A Novel Regulatory Factor Recruits the Nucleosome Remodeling Complex to Wingless Integrated (WNT) Signaling Gene Promoters in Mouse Embryonic Stem cells.

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Public Summary:
This is an important milestone paper in stem cell research in that the gene that was initially discovered in oral cancer development in the hamster cheek pouch model (DOC-1, CDK2AP1) is now a regulator of guiding the landing of the nucleosome remodeling complex (NuDR) to master stem cell genes in the WNT signaling pathway. This paper provides comprehensive biological interactions among NuRD, Wnt signalling, and mESC differentiation in a global genomic context. The interaction map uncovers new gene coexpression patterns, which modulate stem cell pluripotency. Taken together, we propose a model that there is an essential auxiliary component, CDK2AP1, that aids the association of the NuRD complex to specific promoters and mediate epigenetic regulation of regions of importance in controlling genes responsible for stem cell pluripotency. Previously, others have shown the role of Wnt and p-β-catenin in stem cell pluripotency and differentiation potential. In fact, there have been controversies surrounding the exact role that Wnt may play in ESCs. Here, we have demonstrated that maintenance of mESC pluripotency is under epigenetic control of the Wnt pathway. Moreover, we observed the site- specific role of MBD3 with a complex interplay of CDK2AP1 on the promoters of Wnt singling genes. We also presented for the first time unique gene signatures responsible in Wnt signalling, differentiation, and nucleosome remodelling useful in defining the biological pathways involved in stem cell identity. We believe elucidating this link between NuRD, Wnt, and differentiation may enable us to ultimately control self-renewal in embryonic stem cells. Furthermore, understanding Wnt controlled stem cell pluripotency and the role of CDK2AP1-MBD3-NuRD complex at the molecular level may largely contribute to current knowledge of basic stem cell biology as well as future application to regenerative therapies.

Scientific Abstract:
Nucleosome Remodeling and Deacetylation (NuRD) complex is required for modulating the transcription of essential pluripotency genes in ESC self-renewal. MBD3 is considered a key player in the formation of a functional NuRD complex. The recruitment of MBD3 to methylated promoters may require other prerequisite factors. We show that Cyclin Dependent Kinase 2-Associated Protein 1 (CDK2AP1), an essential gene for early embryonic development, plays a role in pluripotency of ESC by engaging MBD3 to the promoter region of Wnt signalling genes. The occupancy of MBD3 on several promoters of Wnt genes was significantly lost in the absence of CDK2AP1, resulting in hyper-activation of Wnt. We propose that the transcriptional modulation of Wnt pathway mediated by NuRD requires the presence of essential auxiliary components, such as CDK2AP1, that may aid the association of the complex with the specific focal region of the target promoters.